Monodentate secondary phosphine oxides (SPO's), synthesis and application in asymmetric catalysis

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Chapter 4

Platinum (II)- catalyzed hydrolysis of nitriles with SPO's as ligands*

This chapter describes the Pt(II)- and Pd(II)- catalyzed hydrolysis of nitriles using racemic or enantiopure secondary phosphine oxides (SPO's) as ligands. The complexes were studied by ^{31}P NMR and X-ray crystallography. Simple nitriles, sterically hindered nitriles, nitriles with acid- or base- sensitive groups and dinitriles were hydrolyzed with preformed catalysts or in situ prepared catalysts, respectively. The proposed mechanism of this reaction is also discussed. Attempts to achieve kinetic resolution of nitriles failed due to the racemization of the ligand, as was established by chiral HPLC-MS.

Contents

* Part of this chapter has been published, see: Jiang, X.-B.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. *J. Org. Chem.* **2004**, *69*, 2327.

4.1 Introduction

For a detailed review of nitrile hydrolysis, see chapter 2.

4.1.1. Classical methods --- Strong acid or base

The hydrolysis of nitriles to amides and carboxyl acids is a very important transformation in organic chemistry.[1] Frequently used methods for nitrile hydrolysis to amides are strong acid (96% H_2SO_4) or base (50% KOH/*t*-BuOH). However, in general, selective hydrolysis of nitriles to amides is troublesome and yields are reasonable at best.

4.1.2. Enzymatic methods[2]

Enzymes are known to be able to convert nitriles to amides or acids. The enzymes used in the hydrolysis of nitriles can be divided into "nitrile hydratases (NHase)" and "nitrilases". A number of enzymes that can catalyze the asymmetric hydrolysis or dynamic kinetic resolutions of nitriles are known. Although many successful applications have been reported, there are still a number of disadvantages related to the enzymatic method. Most enzymes are quite sensitive to the variation in structure of the nitriles and the reaction conditions. Slow reaction rate and low conversion are some of the problems encountered, and sometimes, reproducibility.

4.1.3. Transition metal based catalysts

Several heterogeneous catalysts[3] based on Cu[4], zeolites[5, 6] and metal oxides[7,8] can catalyze the hydrolysis of nitriles to amides. However, the yields are low (<20%). As an alternative to heterogeneous catalysts in the hydrolysis of nitriles to amides, homogeneous catalysts[9] have been used in this process and these prove to be much more effective and selective. For the comparison of selective homogeneous catalysts for the hydrolysis of acetonitrile, see chapter 2.

In summary, only a few good methods for the hydrolysis of nitriles to amides under neutral conditions are available. The classic method needs harsh reaction conditions, which exclude the presence of most functional groups. The enzymatic method is sensitive to the variation of conditions and in several cases low yields. The heterogeneous catalysts gave low yields. The homogeneous catalysts had several successful examples; however, the selectivity is a major problem. Among them, platinum SPO's complexes are effective catalysts for the hydrolysis of nitriles to amides. Our goal is to prepare catalysts based on racemic and enantiopure SPO's, study their complexes by NMR or X-ray crystallography, broaden their application in the hydrolysis of various nitriles and attempt to achieve kinetic resolution of racemic nitriles. The preparation of the enantiopure SPO's was described in chapter 3.

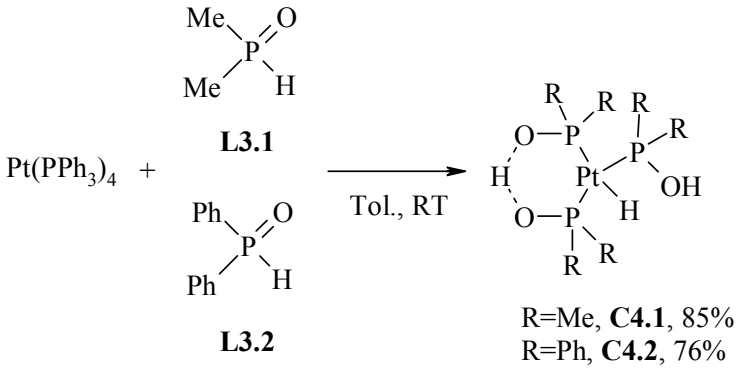
4.2 Characterization of Platinum complexes with SPO's

4.2.1 Platinum complexes with SPO's

(a) Racemic SPO's

In order to establish the methodology for the preparation of the chiral catalysts, we first studied the properties of platinum and palladium complexes with racemic SPO's as ligands.

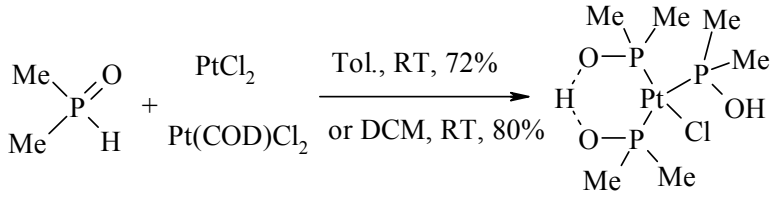
As test examples, we prepared catalysts **C4.1** and **C4.2** from $Pt(PPh_3)_4$ and 5 eq. of **L3.1** (Me_2PHO) or **L3.2** (Ph_2PHO) in toluene following the literature procedure.[10] Although the preparation starts with Pt(0), the metal is *in situ* oxidized to Pt(II) by the SPO ligands at RT (Scheme 4.1). The driving force of this reaction might be the poor solubility of the formed catalysts **C4.1**, **C4.2** in most organic solvents.



Scheme 4.1 The synthesis of catalysts **C4.1**, **C4.2**

However, with the related unsymmetrical ligands, such as racemic **L3.4** (*t*-BuPhPHO), this procedure failed to give the analogous complex. It seems that this procedure only works for the symmetrical SPO's such as **L3.1** (Me_2PHO) or **L3.2** (Ph_2PHO), whereas for unsymmetrical SPO's, no desired product could be isolated.

$Pt(PPh_3)_4$ is quite expensive, air and light sensitive, thus difficult to handle. For these reasons we explored the preparation of complexes starting from $PtCl_2$ or $Pt(COD)Cl_2$ as metal precursors instead of $Pt(PPh_3)_4$. Gratifyingly, reaction of $PtCl_2$ with 5 eq. of **L3.1** (Me_2PHO) in toluene for 2 days gave a white solid, which was crystallized from DCM:Et_2O, 3:1 to give **C4.3** as colorless needles (Scheme 4.2). Its structure was elucidated by X-ray analysis and turned out to be similar to **C4.1** (see figure 4.6). With the more soluble $Pt(COD)Cl_2$ and 5 eq. **L3.1** (Me_2PHO) in DCM, the reaction is finished overnight and affords the same product.



L3.1 **C4.3**

Scheme 4.2 The synthesis of catalyst **C4.3**

It was found later that *in situ* preparation of the catalysts by using $PtCl_2$ in combination with 3-4 eq. of racemic SPO's **L3.1**, **L3.4** or enantiopure **L3.4** gave platinum phosphorus complexes (complicated in ^{31}P NMR spectra), which could not be isolated as single species. However, they show high activities, which are comparable to those of the preformed catalyst **C4.1** in the hydrolysis of some nitriles. The active species structurally similar to **C4.1** are probably formed *in situ*, however, no induction period was observed.

$PdCl_2$ or $Pd(COD)Cl_2$ can also react with SPO's like **L3.1**, **L3.4** to give complexes, which could not be isolated as single compounds. The *in situ* prepared Pd complexes show somewhat lower activities compared to their platinum analogues in the hydrolysis of nitriles.

Racemic dialkyl phosphites like $(EtO)_2PHO$ are structurally similar to SPO's and these ligands can also form complexes with platinum. However, the isolated Pt phosphite complexes did not show any activity in the nitrile hydrolysis.

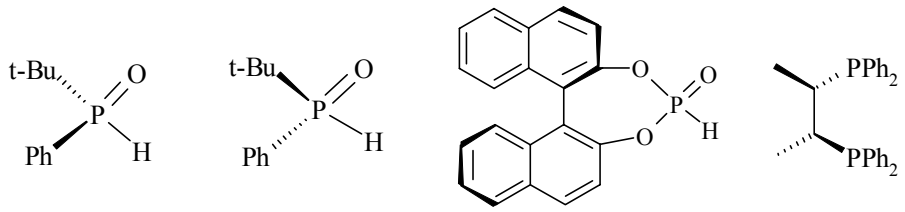
(b) Enantiopure ligands

In an attempt to prepare chiral platinum catalysts, different types of ligands such as chiral phosphines, SPO's, phosphites, bisoxazolines or their combinations were tested. With both enantiomers of ligand **L3.4**, the procedure shown in scheme 4.2 failed to give a single product. ^{31}P NMR showed the presence of several Pt-complexes, but this mixture didn't show any activity in nitrile hydrolysis.

Enantiopure phosphite **4.1** (see figure 4.1) based on (*S*)-binol reacted with $Pt(PPh_3)_4$ in toluene to give a grey-white powder which precipitated from the solution. ^{31}P NMR did confirm the presence of a platinum complex with a coupling constant $J_{Pt\text{-}P}$ of 3674 Hz. Presumably, two ligands of **4.1** are *cis* to each other when coordinating to Pt, but the structure could not be established. Furthermore, no activity was found in nitrile hydrolysis.

Bidentate ligands are known to form stable complexes with metal precursors because of their rigidity.[11] The chiral bidentate phosphine ligand bdpb (chiraphos) [(*2R*, *3R*)-(+)-bis(diphenylphosphino)butane] (Figure 4.1) as well as a combination of bdpb with **L3.1** (Me_2PHO) were also examined. Bdpb reacted with $Pt(PPh_3)_4$, $PtCl_2$ or $Pt(COD)Cl_2$ to give a similar platinum complex[12] based on ^{31}P NMR data, but no

activity in nitrile hydrolysis was observed. The Pt complex was then reacted with $AgBF_4$ to remove the chloride prior to the addition of **L3.1**. However, the desired hybrid cationic complex was not obtained; and the platinum bdpb complex remained unchanged according to ^{31}P NMR. The resulting mixture did not show any activity in nitrile hydrolysis. Attempts to exchange ligands between bdpb and **C4.1** in the Pt-bdpb complex failed, which might be due to the poor solubility of **C4.1** in most organic solvents.



(*S*)-(-)- L3.4 **(*R*)-(+)-L3.4** **4.1** **bdpb**

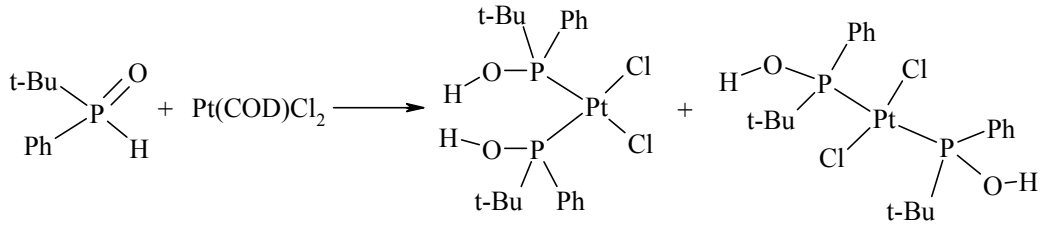
Figure 4.1 Structures of some chiral ligands

4.2.2 NMR study of platinum / SPO coordination chemistry

All the platinum phosphorus complexes presented in the previous part have been studied mainly by ^{31}P NMR except when they could be analyzed by X-ray crystallography. As the solubility of $Pt(COD)Cl_2$ is far better than $PtCl_2$ in most organic solvents, the NMR study of platinum complexes with SPO's or other ligands has been performed mainly with $Pt(COD)Cl_2$ as the metal source.

Platinum has isotopes ^{195}Pt and ^{196}Pt and they split the phosphorus NMR signal to a triplet with one major and two small satellite peaks in the complexes. The structure of these complexes can be elucidated from the *J* values of the coupling constants between platinum and phosphorus. When the two phosphorus atoms in the complex are *trans* to each other, the $J_{Pt\text{-}P}$ value is around 2500 Hz. For the *cis* complex, the $J_{Pt\text{-}P}$ value is around 4000 Hz.[13]

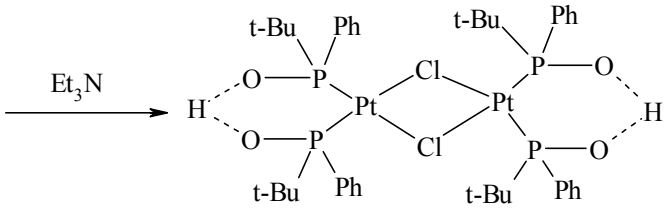
$Pt(COD)Cl_2$ was added to a solution of excess racemic or enantiopure **L3.4** in DCM at RT and the reaction monitored by ^{31}P NMR. Initially, a mixture of *cis* **4.2** and *trans* **4.3** complexes in a ratio of 3:2 is formed (see figure 4.2-4.5). After treatment with Et_3N, one proton of **L3.4** is removed and a new dimeric platinum complex **4.4** is formed exclusively (Scheme 4.3). This process is irreversible.



L3.4

ratio 3 (*Cis*) : 2 (*Trans*)

4.2 **4.3**



Scheme 4.3 Reactions between $Pt(COD)Cl_2$ and racemic or enantiopure **L3.4**

It was found that racemic **L3.4** forms a mixture of *trans*-meso [(*R,R*) and (*S, S*)] and *trans*-racemic [(*R,S*) and (*S,R*)] and *cis*-meso [(*R,R*) and (*S,S*)] and *cis*-racemic [(*R,S*) and (*S,R*)] complexes [^{31}P NMR: *trans*, δ 86.1 (d), $J_{Pt\text{-}P}$ = 2492 Hz; *cis*, δ 82.8 (d), $J_{Pt\text{-}P}$ = 4081 Hz, see figure 4.2], whereas with enantiopure (*R*)-(+)-**L3.4**, a mixture of *trans*-(*R,R*) and *cis*-(*R,R*) complexes were formed during this process [^{31}P NMR: *trans*, δ 85.8 (s), $J_{Pt\text{-}P}$ = 2492 Hz; *cis*, δ 82.5 (s), $J_{Pt\text{-}P}$ = 4023 Hz, see figure 4.4]. After treatment with Et_3N, dimeric complexes **4.4** are formed. With racemic **L3.4**, the ^{31}P NMR of the complex **4.4** shows double peaks as it is C_2-symmetrical and maybe it is impossible to have two *t*-Bu groups on the same side in the six-membered ring complex (e.g. 1,3 diaxial interaction) [^{31}P NMR: δ 61.3 (d), $J_{Pt\text{-}P}$ = 3982 Hz, see figure 4.3]. When (*R*)-(+)-**L3.4** was used, only a single peak was formed [^{31}P NMR: δ 63.1 (s), $J_{Pt\text{-}P}$ = 3982 Hz, see figure 4.5]. However, it was found later that these complexes show little or no activity in the hydrolysis of nitriles.

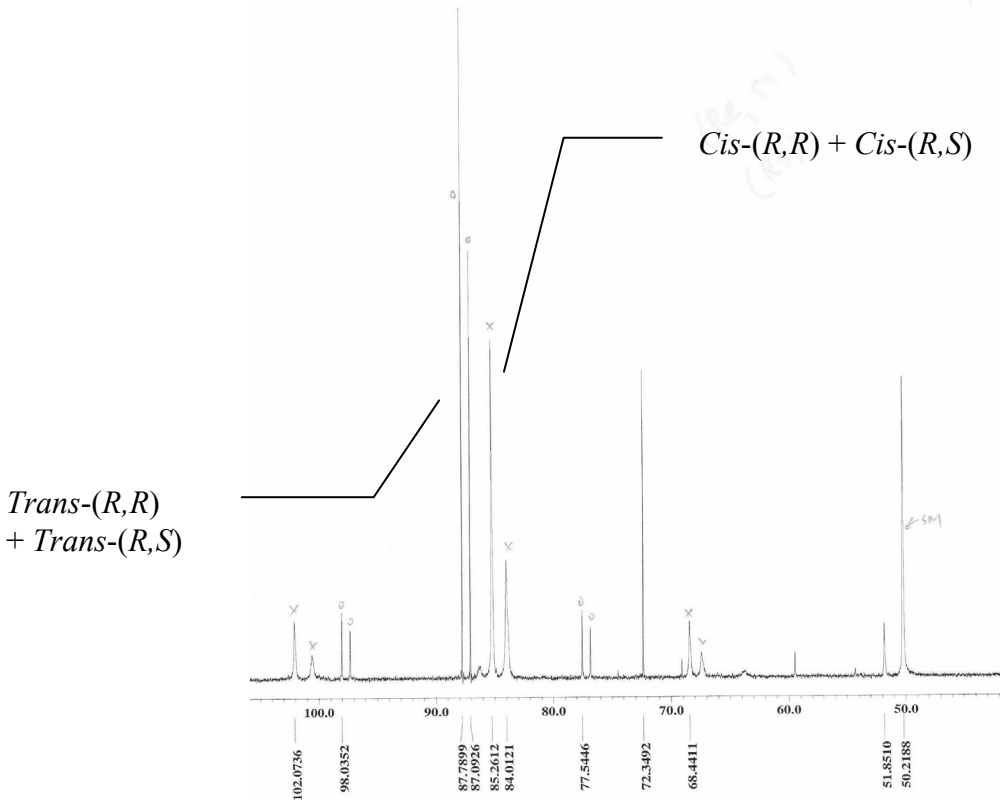


Figure 4.2 ^{31}P NMR ($CDCl_3$) spectrum of complex of $Pt(COD)Cl_2$ and racemic **L3.4**

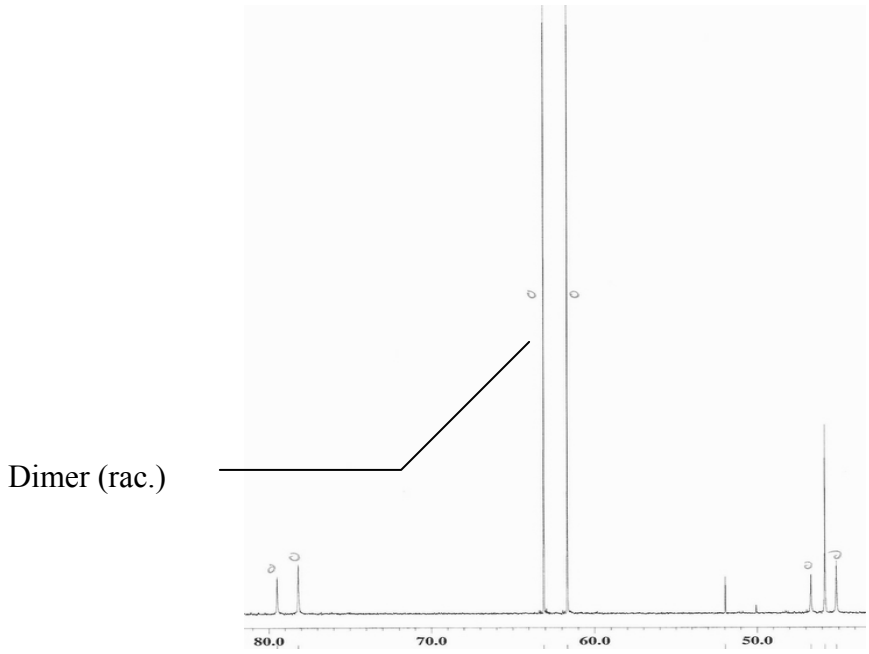


Figure 4.3 ^{31}P NMR ($CDCl_3$) spectrum of complex of $Pt(COD)Cl_2$ and racemic **L3.4** after treatment with Et_3N

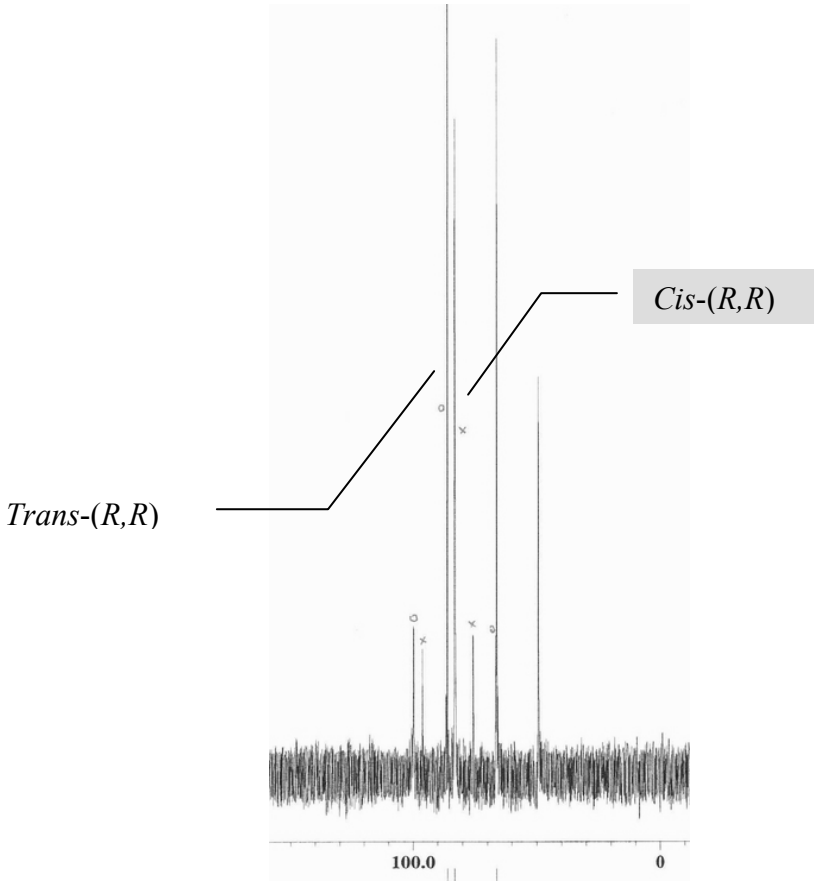


Figure 4.4 ^{31}P NMR ($CDCl_3$) spectrum of complex of $Pt(COD)Cl_2$ and (*R*)-(+)-**L3.4**

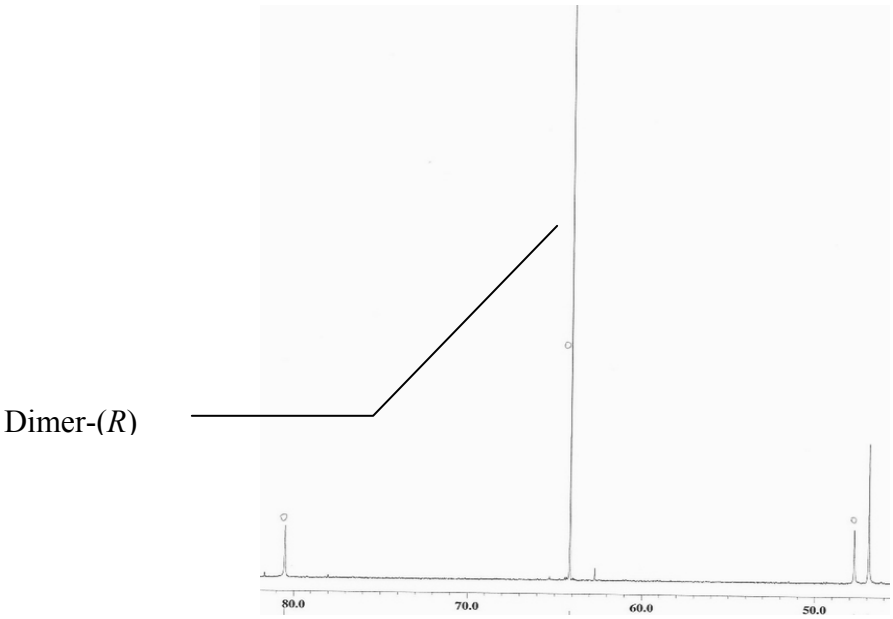


Figure 4.5 ^{31}P NMR ($CDCl_3$) spectrum of complex of Pt(COD)Cl_2 and (*R*)-(+)-**L3.4** after treatment with Et_3N

It was found that the complex of $PtCl_2$ and *trans* racemic cyclic SPO (**L3.3**, structure see chapter 3) forms a mixture of (*R,S*)/(*S,R*) and (*R,S*)/(*R,S*) complexes with a $J_{Pt\text{-}P}$ value of 2648 Hz, which indicates that the ligands are *trans* to each other in the complex. With enantiopure **L3.3**, only one stereoisomer of the corresponding Pt-complex is formed.

Other platinum and SPO's complexes such as preformed catalysts **C4.1**-**C4.3** have a $J_{Pt\text{-}P}$ around 2500Hz. At ambient temperature, the three SPO ligands can exchange with each other, but one ligand always coordinates with platinum.[10b] The observed coupling constants indicates the ligand is *trans* to H or Cl in these complexes.

4.2.3 X-ray structure of platinum complex

$PtCl_2$ was reacted with 5 eq. of **L3.1** (Me_2PHO) in toluene at RT for 2 days. At first, $PtCl_2$ slowly dissolved and finally a white solid precipitated from the solution. Crystallization from DCM : Et_2O, 3:1 gave **C4.3**[14] as colorless needles which were suitable for X-ray analysis (Figure 4.6). Later, it was found that using the more soluble Pt(COD)Cl_2 and 5 eq. of **L3.1** (Me_2PHO) in DCM, the reaction is much faster and finished overnight to give the same product **C4.3** (see scheme 4.2).

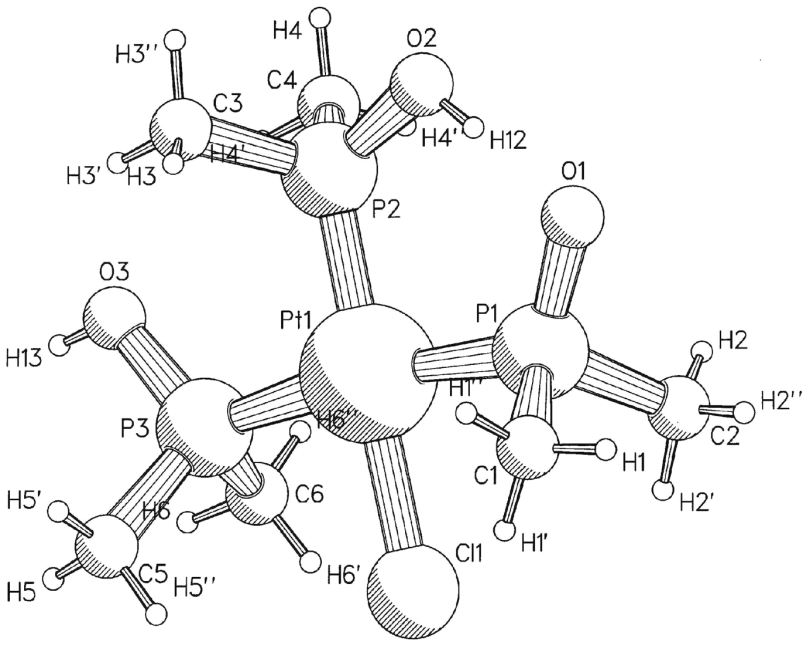


Figure 4.6 A perspective PLUTO drawing of the X-ray structure of **C4.3**

The X-ray analysis shows that the structure of **C4.3** is [PtCl(PMe_2OH)(PMe_2 O…H…$OPMe_2$)], which is comparable to the structure of **C4.1** (see scheme 4.1).
The platinum in the structure of **C4.3** is square planar coordinated to 3 SPO ligands, the angles between P(2)-Pt(1)-Cl(1), P(3)-Pt(1)-P(1) are 178.98° and 170.93°, respectively (Table 4.2). In particular, it shares with **C4.1** the deprotonation of one of the hydroxyl groups of the Me_2PO. From the position of two oxygen atoms O1 and O2 observed in the X-ray structure, we assume they share one hydrogen, as the catalyst itself is neutral. The P-O^- is hydrogen-bonded to the adjacent Me_2PHO. For example, in figure 4.6, the distance of O(1)-O(2) is 2.446(4) Å, which is typical for a hydrogen bond between the oxygens[15] and angle between O(1)-H(12)-O(2) is 178°. Meanwhile, the intermolecular hydrogen bond between O(3)-H(13)-O(1) is also observed (Table 4.1).

Table 4.1 Geometry and distance of intra- and intermolecular hydrogen bonds (Å, °) with *e.s.d.*'s in parentheses

D-H…A	[ARU-code]	D-H (Å)	H…A (Å)	D…A (Å)	D-H…A (°)
O2-H12…O1	[ ]	0.82	1.63	2.446(4)	178
O3-H13…O1	[8455.01]	0.82	1.78	2.593(4)	169

Note: translation of ARU-code to equivalent position code: [8455.] = -1/4+x,-1/40-y,3/4+z. An intermolecular hydrogen bond formed between O3-H13 and another molecular of **C4.3**.

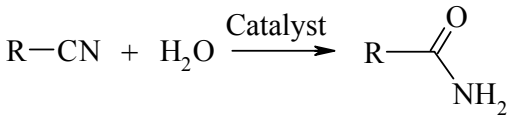
Details of some selected bond distances, angles and torsion angles are listed in table 4.2.

Table 4.2 Selected bond distances (Å), angles and torsion angles (°) of **C4.3** with estimated standard deviations (*e.s.d.'s*) in parentheses

Bond distances (Å)			
Pt(1)-Cl(1)	2.3814(10)	P(2)-O(2)	1.573(3)
Pt(1)-P(1)	2.3164(10)	P(2)-C(3)	1.797(5)
Pt(1)-P(2)	2.2259(10)	P(2)-C(4)	1.797(5)
Pt(1)-P(3)	2.3291(10)	P(3)-O(3)	1.590(4)
P(1)-O(1)	1.554(3)	P(3)-C(5)	1.798(5)
P(1)-C(1)	1.796(5)	P(3)-C(6)	1.790(5)
P(1)-C(2)	1.797(4)	O(1)-O(2)	2.446(4)
Bond angles & torsion angles (°)			
Cl(1)-Pt(1)-P(1)	85.59(4)	Pt(1)-P(2)-O(2)	116.07(12)
Cl(1)-Pt(1)-P(2)	178.98(4)	Pt(1)-P(2)-C(3)	113.83(17)
Cl(1)-Pt(1)-P(3)	85.06(4)	Pt(1)-P(2)-C(4)	113.07(16)
P(1)-Pt(1)-P(2)	94.09(4)	O(2)-P(2)-C(3)	103.6(2)
P(1)-Pt(1)-P(3)	170.93(4)	O(2)-P(2)-C(4)	104.20(19)
P(2)-Pt(1)-P(3)	94.95(5)	C(3)-P(2)-C(4)	104.9(2)
Pt(1)-P(1)-O(1)	117.80(12)	Pt(1)-P(3)-O(3)	115.89(13)
Pt(1)-P(1)-C(1)	111.08(15)	Pt(1)-P(3)-C(5)	113.49(16)
Pt(1)-P(1)-C(2)	112.20(14)	Pt(1)-P(3)-C(6)	111.74(16)
O(1)-P(1)-C(1)	105.99(19)	O(3)-P(3)-C(5)	104.7(2)
O(1)-P(1)-C(2)	105.4(2)	O(3)-P(3)-C(6)	106.0(2)
C(1)-P(1)-C(2)	102.2(2)	C(5)-P(3)-C(6)	104.0(3)
Cl(1)-Pt(1)-P(1)-O(1)	-178.29(17)	Cl(1)-Pt(1)-P(1)-C(1)	-55.81(17)
Cl(1)-Pt(1)-P(1)-C(2)	59.12(16)	P(2)-Pt(1)-P(1)-O(1)	2.73(17)
P(2)-Pt(1)-P(1)-C(1)	125.21(17)	P(2)-Pt(1)-P(1)-C(2)	-119.86(17)
P(1)-Pt(1)-P(2)-O(2)	0.87(14)	P(1)-Pt(1)-P(2)-C(3)	-119.24(19)
P(1)-Pt(1)-P(2)-C(4)	121.22(18)	P(3)-Pt(1)-P(2)-O(2)	-178.44(14)
P(3)-Pt(1)-P(2)-C(3)	61.45(19)	P(3)-Pt(1)-P(2)-C(4)	-58.08(18)
Cl(1)-Pt(1)-P(3)-O(3)	175.25(17)	Cl(1)-Pt(1)-P(3)-C(5)	54.1(2)
Cl(1)-Pt(1)-P(3)-C(6)	-63.2(2)	P(2)-Pt(1)-P(3)-O(3)	-5.77(17)
P(2)-Pt(1)-P(3)-C(5)	-127.0(2)	P(2)-Pt(1)-P(3)-C(6)	115.8(2)

4.3 Platinum and palladium catalyzed hydrolysis of nitriles

After the synthesis of the preformed catalysts, they were tested in the hydrolysis of various nitriles. The *in situ* formed catalysts and enantiopure ligands were also tested (Scheme 4.4).



Scheme 4.4 The hydrolysis of nitriles with platinum or palladium catalysts

4.3.1 Simple nitriles

In a test reaction, acetonitrile and α-methylbenzyl cyanide **4.5** (Scheme 4.7) were applied as model substrates in the hydrolysis reactions with the preformed catalysts **C4.1**, **C4.2** and **C4.3**.

In the hydrolysis of acetonitrile, catalysts **C4.1**, **C4.2** and **C4.3** all gave full conversions to the corresponding amide as the sole product, **C4.1** being the most active catalyst. Their catalytic activities decrease as following: **C4.1**>**C4.3**>**C4.2**. With 0.5 mol% of **C4.1**, the reaction took 3 h at 80 ^{o}C in EtOH/H_2O whereas using **C4.3**, a reaction time of 24 h was required. With 1.8 mol% of catalyst **C4.2**, 58 h was needed for complete conversion. When **4.2** was used as substrate, similar trends were found. The somewhat reduced rate of **C4.3** is due to the presence of the chloride anion, which can still compete with the nitrile for the Pt-binding site.

Some *in situ* formed catalysts were also examined. The combination of $PtCl_2$ and Me_2PHO (**L3.1**), $PtCl_4$ and Me_2PHO (**L3.1**), $PtCl_2$ and *trans* cyclic **L3.3**, $PtCl_2$ and (*R*)-(+)-*t*-BuPhPHO (**L3.4**), $[Rh(COD)Cl]_2$ and **4.1** (see figure 4.1) were used as catalysts in the hydrolysis. The results are shown in table 4.3.

Table 4.3 The results of the hydrolysis of simple nitriles [a]

Entry	Catalysts	Nitriles	Cat. (mol%)	t (h)	Products	Yields (%) [b]
1	**C4.1**	**4.5**	0.5	3	**4.6**	95
2	**C4.2**	**4.5**	1.8	58	**4.6**	86
3	**C4.3**	**4.5**	0.5	24	**4.6**	84
4	$PtCl_2$ + **L3.1**	CH_3CN	0.3	24	CH_3CONH_2	85
5	$PtCl_4$ + **L3.1**	CH_3CN	0.2	24	CH_3CONH_2	18 [c]
6	$PdCl_2$ + **L3.1**	**4.5**	2	24	**4.6**	91
7	$PtCl_2$ +(*R,S*)-**L3.3**	**4.5**	2	40	**4.6**	55
8	$PtCl_2$ + *R*-(+)-**L3.4**	**4.5**	2	18	**4.6**	93
9	$PdCl_2$ + *R*-(+)-**L3.4**	**4.5**	2	6	**4.6**	90
10	$PdCl_2$ + *R*-(+)-**L3.4**	**4.5**	5	30	**4.6**	55 [c, d]
11	K_2PtCl_4 + *R*-(+)-**L3.4**	**4.5**	2	28	**4.6**	35 [c]
12	$[Rh(COD)Cl]_2$ + **4.1**	**4.5**	2	24	**4.6**	17 [c]
13	$PtCl_2$ + **4.1**	**4.5**	2	18	**4.6**	16 [c]

a. General conditions: 5 mmol of nitrile, 4 ml of EtOH, 2 ml of H_2O, at 80 ^{o}C. b. Isolated yields. c. Conversion. d. RT.

From these results, it can be concluded that *in situ* formed catalysts are quite effective in the hydrolysis of simple nitriles. The combinations of $PtCl_2$ or $PdCl_2$ and **L3.1** are much more active than the combination of $PtCl_4$ and **L3.1** and $[Rh(COD)Cl]_2$ and **4.1** (table 4.3, entry 4-6, 12). It also shows somewhat higher activity than $PtCl_2$ and *(R,S)*-**L3.3** (table 4.3, entry 7). The combination of $PtCl_2$ and phosphite **4.1** has low activity in the hydrolysis of **4.5** (table 4.3, entry 13), whereas with its palladium analogue, only about 4% conversion was found.

Attempts to achieve kinetic resolution of **4.5** failed. In the hydrolysis with the *in situ* catalysts made from $PtCl_2$ and (*R*)-(+)-**L3.4**, *(R,S)*-**L3.3** and **4.1**, respectively, both the product **4.6** and the remaining **4.5** were racemic at several stages of conversion (16%-100%) (table 4.3, entry 7-13). Likewise, the combination of $PdCl_2$ and *(R)*-(+)-**L3.4** did catalyze the hydrolysis of **4.5** to **4.6** even at RT (table 4.3, entry 10); however, no e.e. was observed neither in **4.5** nor in **4.6**.

Using the *in situ* formed complexes of the more soluble $Pt(COD)Cl_2$ or $Pd(COD)Cl_2$ and **L3.1**, the activities drop substantially as compared to that of the catalysts derived from $PtCl_2$ or $PdCl_2$. This might be due to the interference of strong coordination of COD with the metal. In particular when $Pd(COD)Cl_2$ was used, no hydrolysis occurred in some cases.

In order to expand the scope of this reaction, a number of sterically hindered tertiary nitriles and nitriles containing acid or base sensitive groups (see figure 4.7, 4.9) were hydrolyzed with the catalysts mentioned above.

4.3.2 Nitriles with acid or base sensitive groups

The hydrolysis of nitriles, possessing acid or base sensitive groups, to the corresponding amides in high yields is problematic or even impossible whithout affecting the functional groups, as general methods for nitrile hydrolysis use strong base or acid. The only useful method is based on enzymatic hydrolysis. However, these enzymatic reactions are frequently slow, sensitive to structure variation, difficult to reproduce and often give low yields. Details were discussed in chapter 2.

In our experiments, nitriles **4.7**, **4.9**, **4.11**, **4.13** possessing acid or base sensitive groups were all smoothly converted to the corresponding amides **4.8**, **4.10**, **4.12**, **4.14** (figure 4.7) without any side reactions in excellent yields (table 4.4).

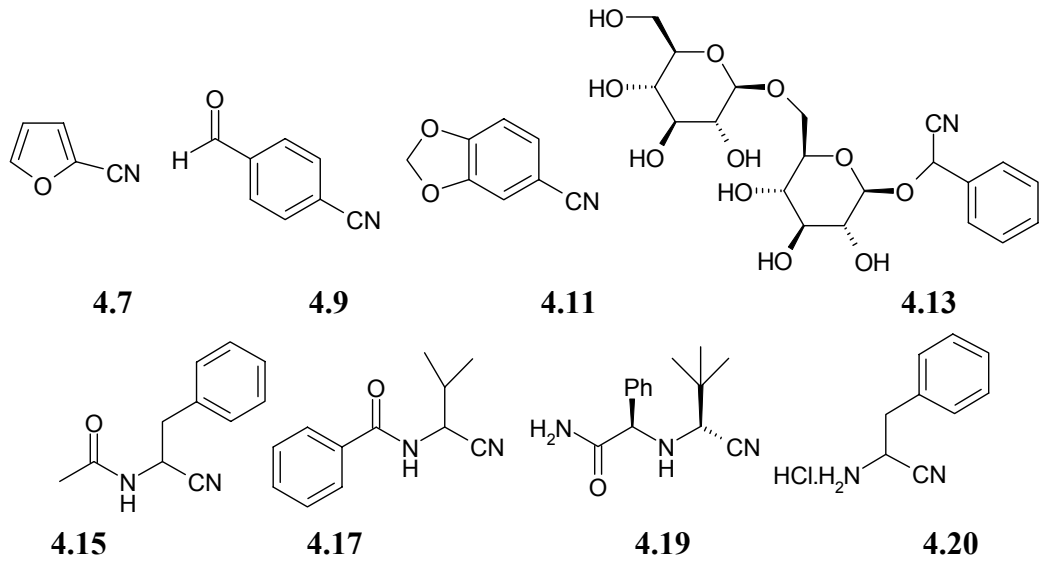


Figure 4.7 The structure of nitriles containing acid or base sensitive groups

Table 4.4 The Pt(II)-catalyzed hydrolysis of nitriles containing acid or base sensitive groups [a]

Entry	Nitrile	Catalyst	T(^{o}C)	t (h)	Product	Yields (%) [b]
1	**4.7**	**C4.1**	80	3.5	**4.8**	96
2	**4.9**	**C4.1**	80	3.5	**4.10**	97
3	**4.11**	**C4.1**	80	3.5	**4.12**	98
4 [c]	**4.13**	**C4.1**	80	4	**4.14**	98
5 [d]	**4.7**	$PtCl_2$ + **L3.4**	80	20	**4.8**	94
6 [d]	**4.7**	**C4.1**	25	20	**4.8**	96
7 [e]	**4.15**	**C4.1**	80	18	**4.16**	94
8 [e]	**4.17**	**C4.1**	80	16	**4.18**	96
9	**4.19**	**C4.1**	80	18	trace	<5
10	**4.20**	**C4.1**	80	18	**-**	0

a. General conditions: 0.5 mol% of catalyst, 5 mmol of nitrile, 4 ml of EtOH, 2 ml of H_2O, at 80 ^{o}C. b. Isolated yields. c. 1 mmol of substrate, pure H_2O as solvent. d. 2 mol% of catalyst. e. 2.5 mol% of catalyst, 0.9 mmol of substrate.

It is even possible to hydrolyze these substrates at room temperature, although a long reaction time was needed (table 4.4, entry 6).

It was found that preformed catalyst **C4.1** is much more reactive than the catalyst formed *in situ* from $PtCl_2$ and **L3.4** (table 4.4, entry 1 and 5).

The nitriles compounds containing amines or protected amides are not easily hydrolyzed. The only method reported in the literature is catalysis by chiral ketones under basic conditions.[16] The aminonitriles first react with chiral ketone to form an imine adduct, then one proton was removed by base to form a 5-member ring imino-oxazolidine intermediate, which was then opened by water to form an imine intermediate following by the hydrolysis of imine to aminoamides and regeneration of the chiral ketone. Several *N*-protected aminonitriles **4.15**, **4.17**, **4.19**, **4.20** were tested in our system. Nitriles **4.15**, **4.17** were smoothly hydrolyzed to the amides **4.16**, **4.18** in excellent yield. However, enantiopure **4.19** was only slowly hydrolyzed to give only a trace of racemic amide; most of the substrate decomposed. Nitrile **4.20** was not converted at all, which might be due to HCl salt acting as poison on the catalyst (the free amine of **4.20** is not stable in protic solvents). The nitriles **4.19**, **4.20** may undergo retro-Strecker reaction (in protic solvents)[17] under the hydrolysis conditions.

Even the very sensitive cyanohydrin **4.13**, was converted to the amide **4.14** in 98% yield without racemization of any of the stereogenic centers in the sugar moieties. The stereochemical integrity of the product **4.14** was confirmed by COSY and NOESY NMR experiments. From 2D NMR, it can be observed that every hydrogen of the sugar moieties in the product **4.14** is *trans* to the adjacent one (no correlation signal in NOESY) similar as in the substrate **4.13**, which means no epimerisation has occurred (Figure 4.8).

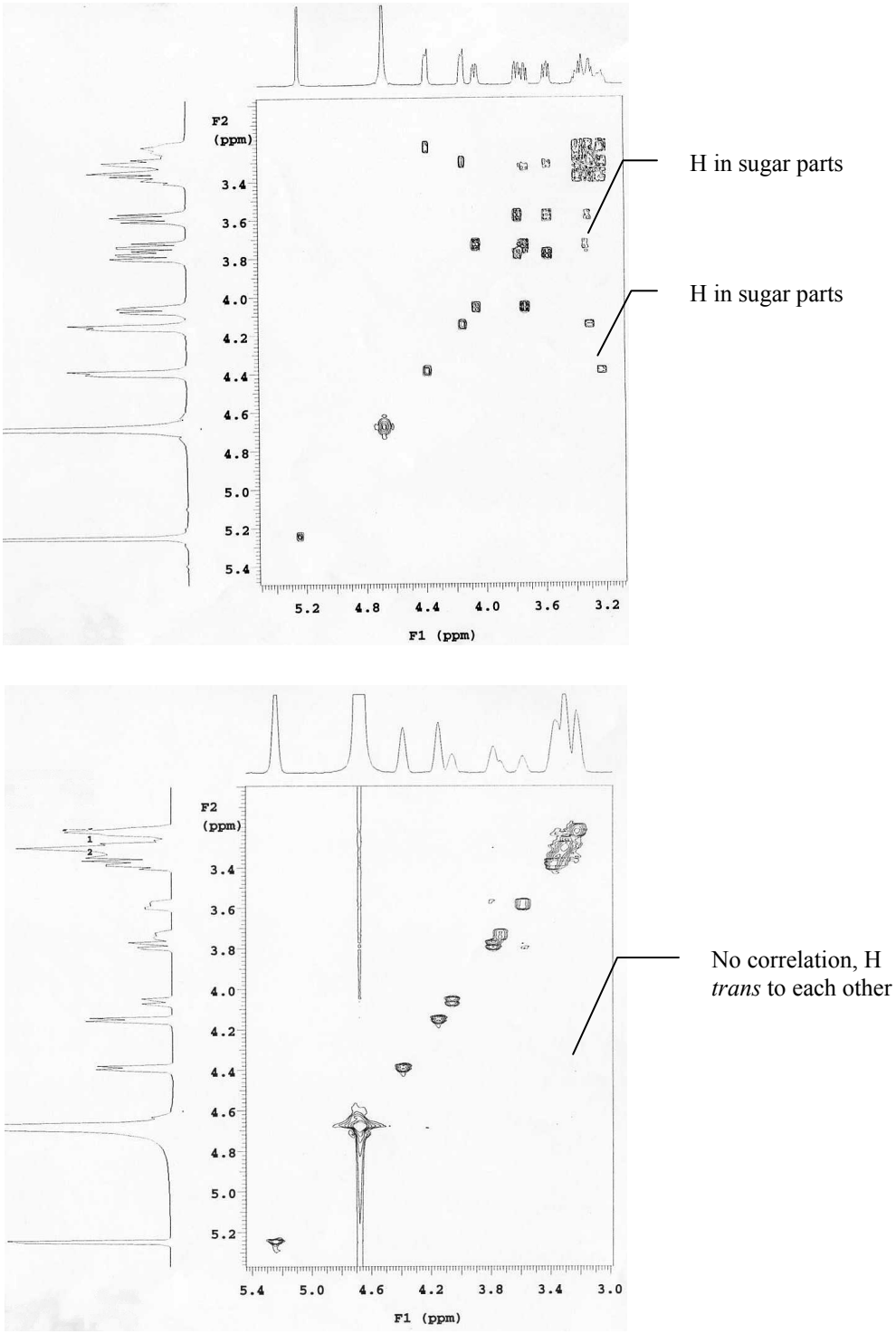


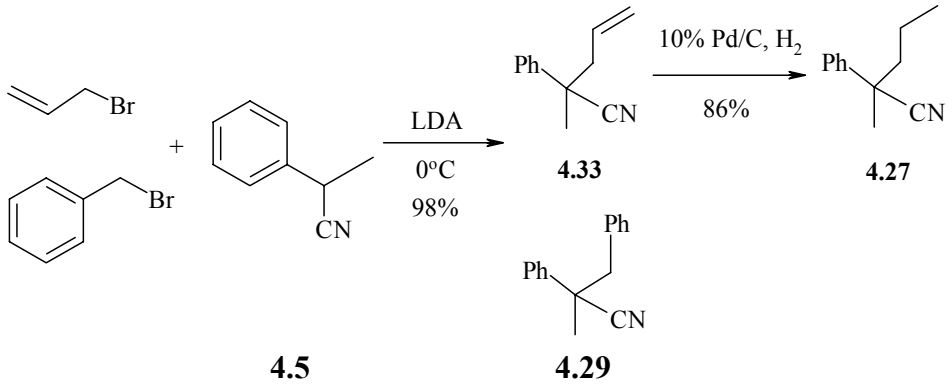
Figure 4.8 COSY and NOESY spectra of **4.14** in D_2O

4.3.3 Tertiary nitriles

Tertiary nitriles are particularly resistant towards hydrolysis. There are only a few successful examples of hydrolysis known in the literature. The use of 96% H_2SO_4 at 140 ^oC for 3 h yields tertiary amides with yields ranging from 10% to 90% depending on the substrate.[18] Strong basic conditions have also been used, but this leads to much lower yields. For instance, *t*-BuCN **4.31** could be converted into trimethyl acetamide

4.32 in 15% yield after 100 h of reflux with 50% KOH in *t*-butanol.[18b] Due to these difficulties, tertiary amides are generally prepared from the corresponding acid chloride and NH_3.[18c,19] Furthermore, the method of Katritzky and co-workers (30% H_2O_2/DMSO/K_2CO_3 at 0°C) does not work for tertiary nitriles.* No efficient method for the hydrolysis of tertiary nitriles has been reported so far.

In view of the above, we decided to further investigate the hydrolysis of tertiary nitriles. In addition, the availability of the enantiopure **L3.4** prompted us to investigate the possibility of kinetic resolution of racemic nitriles. In order to exclude any possible racemization of the nitriles or amides, substituents are introduced into the benzylic position of the nitrile **4.5** to afford tertiary nitriles **4.29** and **4.33** (Scheme 4.5). However, nitrile **4.33** could not be hydrolyzed with the catalysts mentioned above, which might be due to strong coordination of the allyl group to the platinum. Therefore, this nitrile was hydrogenated to the saturated nitrile **4.27** with 10% Pd/C and H_2 in 86% isolated yield (Scheme 4.5).



Scheme 4.5 The synthesis of tertiary nitrile **4.27**, **4.29**, **4.33**

In our experiments, several tertiary nitriles **4.21**, **4.23**, **4.25**, **4.27**, **4.29**, **4.31** were selected as substrates for the hydrolysis with preformed or *in situ* formed catalysts (Figure 4.9).

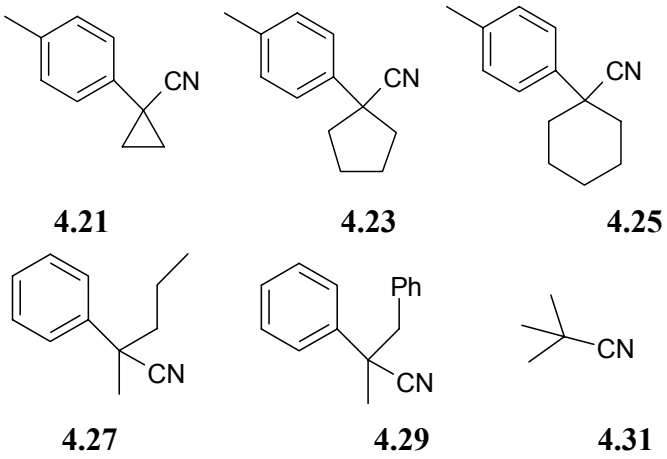


Figure 4.9 The structure of tertiary nitriles

* We found no reaction with nitrile **4.21** in 30% H_2O_2/K_2CO_3/DMSO.

All nitriles (**4.21, 4.23, 4.27, 4.29, 4.31**) except **4.25** were completely converted to the corresponding amides (**4.22, 4.24, 4.28, 4.30, 4.32**) using only 0.5 mol% of catalyst **C4.1** in EtOH /H_2O mixtures at 80 °C (Table 4.5).

Table 4.5 The platinum-catalyzed hydrolysis of tertiary nitriles [a]

Entry	Nitriles	Catalyst	T(^{o}C)	t (h)	Products	Yields (%)[b]
1	**4.21**	**C4.1**	80	5	**4.22**	97
2	**4.23**	**C4.1**	80	12	**4.24**	99
3 [c]	**4.25**	**C4.1**	80	48	**4.26**	95
4 [d]	**4.27**	**C4.1**	80	25	**4.28**	97
5 [d]	**4.29**	**C4.1**	80	35	**4.30**	96
6	**4.31**	**C4.1**	80	41	**4.32**	79
7 [e]	**4.21**	**C4.3**	80	18	**4.22**	90
8 [e]	**4.27**	**C4.3**	80	18	**4.28**	25
9 [e]	**4.21**	**C4.1**	25	90	**4.22**	95
10	**4.21**	**C4.1**	45	27	**4.22**	98
11	**4.23**	**C4.1**	45	59	**4.24**	97
12 [f]	**4.21**	$PtCl_2$ + **L3.4**	80	21	**4.22**	85
13 [f]	**4.23**	$PtCl_2$ + **L3.4**	80	33	**4.24**	74
14 [f]	**4.27**	$PtCl_2$ + **L3.4**	80	48	**4.28**	43
15 [f]	**4.29**	$PtCl_2$ + **L3.4**	80	48	**4.30**	41
16 [g]	**4.21**	**C4.1**	80	6	**4.22**	93

a. General conditions: 5 mmol of nitrile, 0.5 mol% of catalyst, 4 ml of EtOH, 2 ml of H_2O, and heat to 80 ^{o}C. b. isolated yields. c. 3.5 mol% catalyst, 1 mmol substrate. d. 1 mol% catalyst. e. 2 mol% catalyst. f. 4 mol% catalyst. g. recycled catalyst from entry 1.

Nitrile **4.25** remained unchanged with 0.5 mol% of **C4.1** even after prolonged reaction time. Increasing the catalyst loading to 3.5 mol%, however, did result in its hydrolysis to amide **4.26** (table 4.5, entry 3). This sluggish reaction might be due to the conformation of the substrate in which the cyano group occupies an axial position were it suffers severe steric hindrance (e.g. 1, 3-diaxial interaction).

The activities of the catalysts decrease as follows: preformed catalyst **C4.1** > **C4.3** ≥ *in situ* formed complex from $PtCl_2$ and **L3.4** (table 4.5, entry 1, 7, and 12).

All the catalysts seem to be quite sensitive to structural variation and steric hindrance. The catalytic activity drops with the increase of steric hindrance of the different nitriles in the following way: **4.21** > **4.23** > **4.25**; **4.21** > **4.23** > **4.27** (table 4.5, entry 1-5, 7-8, 12-15).

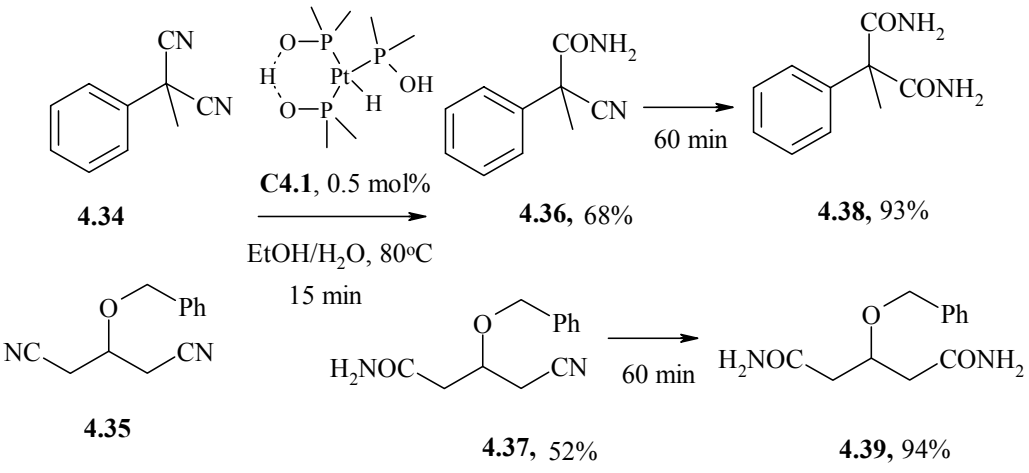
These substrates could even be hydrolyzed at room temperature, although a long reaction time was needed (table 4.5, entry 9). Also, the reaction rate is much slower than the hydrolysis of nitriles with sensitive groups (table 4.4, entry 6).

We found that the products can be extracted cleanly with THF or DCM after evaporating the ethanol/water mixture because of the poor solubility of the catalysts in

most organic solvents. The recycled catalysts could be used at least one more time in subsequent reactions and largely retained their activity (table 4.4, entry 16).
In summary, catalyst **C4.1** is less hindered and more active than **C4.2**, **C4.3** and the *in situ* complexes made from $PtCl_2$ and ligand **L3.4**, especially with the sterically hindered tertiary nitriles. With unhindered nitriles, the difference is less pronounced. Using catalyst **C4.1**, all substrates were smoothly converted to the corresponding amides in over 95% isolated yield except for *t*-BuCN **4.31**. The hydrolysis of unhindered nitriles (**4.7, 4.9, 4.11, 4.13, 4.15, 4.17**) is completed in 3-4 h but the sterically hindered tertiary nitriles (**4.21, 4.23, 4.27, 4.29, 4.31**) need reaction times up to 41 h to give full conversions under these conditions. Increasing the catalyst loading to 2 mol% reduced the reaction time to 5-18 h.

4.3.4 Dinitriles

The nitriles discussed above only contain one cyano group. Besides these nitriles, two di-nitriles **4.34** and **4.35** were tested to see if it is possible to perform selective hydrolysis of one cyano group. The same standard reaction conditions as above were applied.

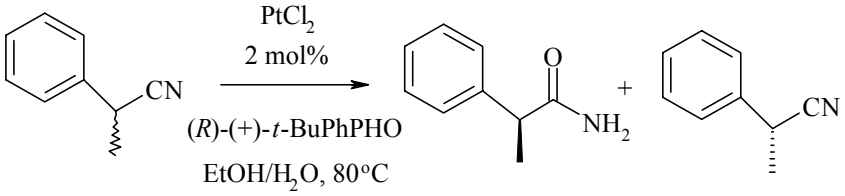


Scheme 4.6 Selective hydrolysis of dinitriles **4.34** and **4.35**

We found that it is possible to control the hydrolysis of only one cyano group in di-nitriles by carefully following the reaction over time. Under standard conditions at 80 ^{o}C, the reactions were fast when the preformed catalyst **C4.1** was used. After 15 min, the hydrolysis of the first cyano group was already finished to give **4.36** and **4.37** in 68% and 52% isolated yields, respectively. Around 10-15% of di-amides were found by TLC. After 1 h, the second cyano group was also hydrolyzed to give di-amides **4.38** and **4.39** in 93% and 94% isolated yields, respectively (Scheme 4.6). There seems to be no apparent difference in the reaction rate between the hindered **4.34** and linear **4.35** dinitriles.

4.3.5 Attempts to achieve kinetic resolution of nitriles

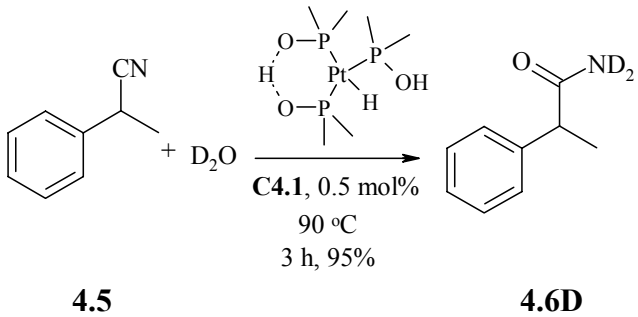
Using platinum complexes based on the enantiopure ligand **L3.4**, kinetic resolution of racemic nitriles was attempted. As we were unable to prepare the PtL_3H or PtL_3Cl complexes from **C4.1**, an *in situ* made catalyst (see section 4.2.1) was examined. Using the *in situ* derived complex from (*R*)-(+)-*t*-BuPhPHO (**L3.4**) and $PtCl_2$, nitrile **4.5** and sterically hindered tertiary nitriles **4.27** and **4.29** were hydrolyzed under the standard conditions. The hydrolysis of **4.27** and **4.29** did not go to completion (55% conversion determined by GC), which might be due to the steric hindrance and deactivation of the catalysts after a long reaction time. Both the e.e. of the remaining substrates and the products were determined during the reaction by chiral HPLC analysis. However in all cases (**4.5**, **4.27, 4.29**) both the nitriles and their product amides **4.6**, **4.28** and **4.30** were found to be racemic at different conversions (20-100%) (Scheme 4.7).



4.5 **4.6**

Scheme 4.7 Attempted kinetic resolution of nitriles **4.5**

To exclude the possibility of racemization of the nitriles or amides an experiment was performed using D_2O instead of H_2O. Upon D-NMR analysis only a signal due to the ND_2 group was observed and no α-deuteration was found neither in the nitrile **4.5** nor in the amide **4.6D** (Scheme 4.8). These findings exclude racemization of the substrates or products.



4.5 **4.6D**

Scheme 4.8 Hydrolysis experiment of **4.5** with catalyst **C4.1** in deuterated solvent

After careful chiral HPLC-MS analysis of the hydrolysis samples we discovered that the ligand (*R*)-(+)-**L3.4** had racemized during the reaction.[20] This explains the disappointing results in the kinetic resolution experiments.

4.3.6 Proposed mechanism

Parkins and co-workers proposed a mechanism for the nitrile hydrolysis.[10a] In this mechanism, the preformed catalyst **C4.1** first forms an adduct **4.40** with water. This complex is in equilibrium with a cationic species **4.41**, which can coordinate with nitriles to form **4.42**. In the cationic complex **4.42** intramolecular attack from the adjacent OH group to the coordinated nitrile occurs to form an imidate intermediate **4.43**. This intermediate **4.43** is attacked by water to form **4.44**; the amides are released from the complex **4.44** and regenerate the active species **4.41** for the next catalytic cycle (Figure 4.10).

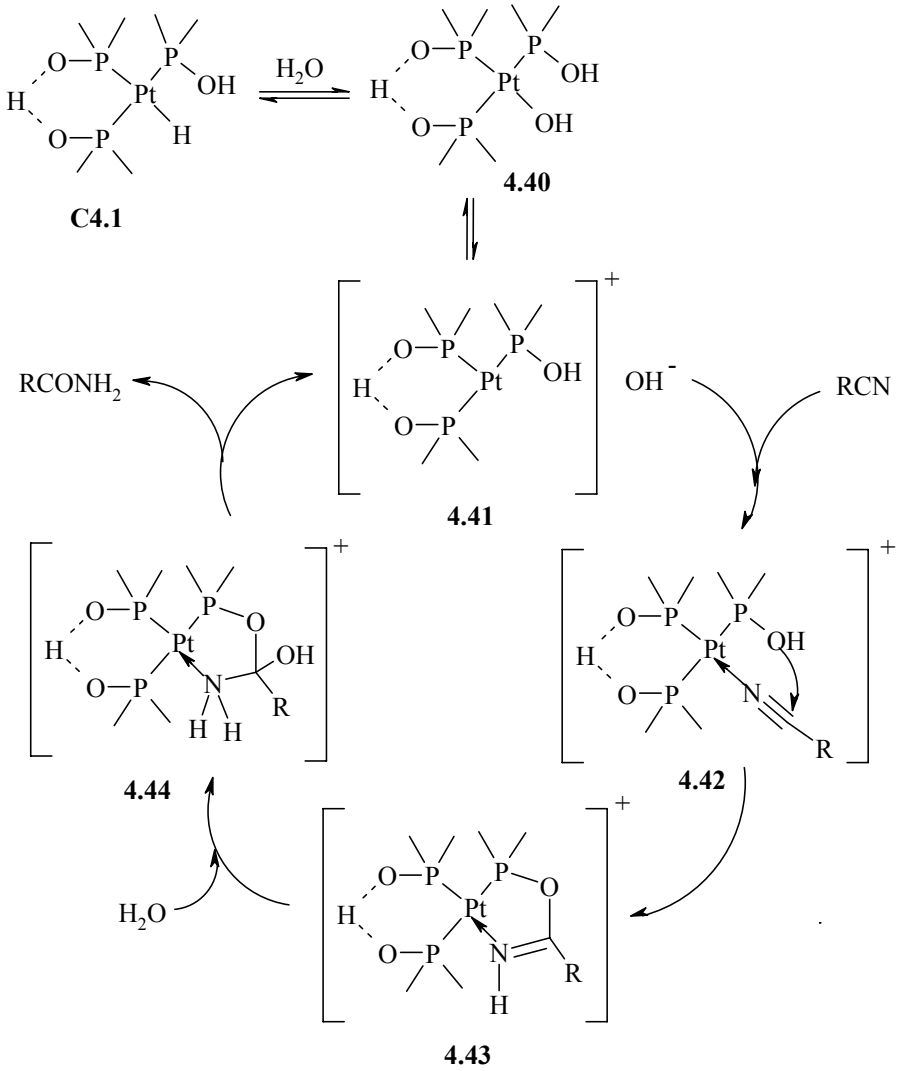


Figure 4.10 Proposed mechanism of nitrile hydrolysis

In support of this mechanism, these authors [10a] found that the activity of the catalyst can be stopped by adding halide ions. Furthermore, the catalytic activity drops dramatically when the adjacent OH group is replaced by a methyl group. It was also found that preformed catalyst **C4.3** itself was not active and can be activated by adding $AgBF_4$ which in situ formed complex proved to be the most active catalyst.

The weakness of this proposed mechanism is that the intermediates have not been isolated and characterized yet.

However, in our experiments, we found that **C4.3** is quite active even without any silver salt (to remove the halide) present. The somewhat lower activity compared to **C4.1** might be due to strong Pt-Cl bond. In the presence of $AgBF_4$, its catalytic activity is still lower than for **C4.1**. The mechanism might be similar to the one discussed above. For the *in situ* formed catalysts, the mechanism is not clear. However, the active species formed during the reaction might be structurally similar to those present when using the preformed catalysts.

4.3.7 Conclusions

In conclusion, by broadening the scope of the nitrile hydrolysis reaction reported by Parkins and coworkers,[10a] a catalytic method has been developed for the hydrolysis of tertiary nitriles and nitriles containing sensitive groups to their corresponding amides. The use of *in situ* formed catalysts is quite successful in the hydrolysis of these nitriles. To the best of our knowledge the excellent yields and chemoselectivities of these reactions are unprecedented in the literature. An attempted kinetic resolution failed and the ligand was found to racemize during the reaction.

4.4 Experimental section

General conditions:

For general conditions, see chapter 3. ^{1}H NMR (300, 500 MHz) and ^{13}C NMR (75.4 MHz) spectra were recorded on a Varian VXR-300, VXR-500 spectrometer in $CDCl_3$, DMSO-d_6 or D_2O. Chemical shifts are recorded in δ units (ppm) relative to the residue deuterated solvent signals of $CDCl_3$ (^{1}H: 7.25 ppm, ^{13}C: 77.0 ppm), DMSO-d_6 (^{1}H: 2.49 ppm, ^{13}C: 39.5 ppm), D_2O (^{1}H: 4.72 ppm). Coupling constants are recorded in Hertz (Hz). Enantiomeric excess (e.e.) of ligand **L3.4**, nitriles **4.5**, **4.27**, **4.29** and amides **4.6**, **4.28**, **4.30** were measured by analytic HPLC (Daicel, chiralpak AD, AS, OD, OJ or OB-H column, 250 x 4.6 mm *i.d., n*-heptane/2-propanol). Gas chromatographic analysis was performed on an HP-1 cross-linked methyl silicone capillary column (25 m x 0.25 mm x 0.25 μm *i.d.*) and a FID detector using He as carrier gas. GC conditions: Init. temp., 100 ^{o}C, 5 min, 10 ^{o}C/min increase, 250 ^{o}C, 15 min, decrease 10 ^{o}C/min to 100 ^{o}C, 0 min. $T_{inl.} = T_{det.} = 250\ ^o$C. Split ratio 75:1.

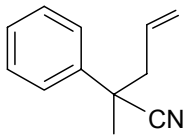
General procedure for the synthesis of nitriles 4.29, 4.33

In a 100 ml round-bottom flask, di-isopropyl amine (55 mmol, 7.7 ml) and dry THF (30 ml) were cooled to 0 ^{o}C. A solution of *n*-BuLi (1.6 M in *n*-hexane, 35 ml, 56 mmol) was added slowly to this ice-cold solution, maintaining the temperature at 0 ^{o}C for 1 h to form a clear light yellow solution. α-Methyl benzylcyanide **4.5** (50 mmol,

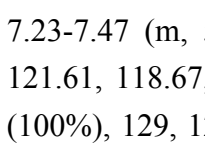
6.7 ml) in dry THF (10 ml) was added, and a yellow turbid solution slowly formed. After 30 min at 0 ^{o}C, a solution of allyl bromide (51 mmol, 4.4 ml) or benzyl bromide (21 mmol, 2.4 ml) and THF (10 ml) were added. The reaction mixture was allowed to warm to RT and stirred overnight. A clear light yellow orange solution was formed. After addition of 30 ml of H_2O, extraction with Et_2O (3 x 100 ml), washing with brine and drying over $MgSO_4$, the solvent was removed under vacuum and the residue purified by flash column chromatography [SiO_2, petroleum ether (40-60 ^{o}C):Et_2O, 2:1] to provide light yellow oils.

2-Methyl-2-phenylpentanenitrile (4.27)[21]

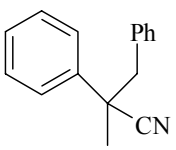
Prepared from α-methyl benzylcyanide **4.5** (50 mmol, 6.7 ml) and allyl bromide (51 mmol, 4.4 ml). Purified by flash column chromatography [SiO_2, petroleum ether (40-60 ^{o}C):Et_2O, 2:1] provide **4.33**[21b-c] as light yellow oil. Isolated yield 98% (8.4 g, 49 mmol). The spectral data were in accordance with the literature.[21b-c] ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3H, CH_3), 2.67 (m, 2H, CH_2), 5.13-5.21 (m, 2H, =CH_2), 5.62-5.83 (m, 1H, =CH), 7.23-7.47 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 138.33, 130.39, 127.38, 126.34, 124.09, 121.61, 118.67, 44.79, 40.66, 25.04. MS (EI^+) 172 (M+1), 171 (M), 145, 131, 130 (100%), 129, 128, 104, 103, 91, 81, 77, 65, 51. HRMS (EI^+) M^+ for $C_{12}H_{13}N$, found 171.1046, calcd. 171.1048.



The above nitrile **4.33** (49 mmol, 8.4 g), 10% Pd/C (1.5 g), absolute EtOH (50 ml) was hydrogenated using a H_2-filled balloon for 24 h at RT. After work-up and removing all the solvent, the residue was passed through a SiO_2 column and eluted with petroleum ether (40-60 ^{o}C):Et_2O, 2:1. After purification by vacuum distillation (71 ^{o}C/2 mbar or 70 ^{o}C/0.14 Torr) (Lit.[21a] 135-145 ^{o}C/2.3 Torr), **4.27**[21a] was obtained as colorless oil. Isolated yield 86% (7.3 g, 42 mmol). ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 6.95 Hz, 3H, CH_3), 1.14-1.26 (m, 1H, CH_2), 1.38-1.52 (m, 1H, CH_2), 1.66 (s, 3H, CH_3), 1.75-1.89 (m, 2H, CH_2), 7.21-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 138.88, 127.34, 126.13, 123.91, 122.07, 42.80, 41.04, 26.24, 17.37, 12.38. MS (EI^+) 174 (M+1), 173 (M), 132, 131 (100%), 130, 129, 117, 116, 104, 103, 91, 77, 65, 51. HRMS (EI^+) M^+ for $C_{12}H_{15}N$, calcd. 173.1205, found 173.1202. GC (250 ^{o}C): t = 9.37 min. HPLC (OB-H, *n*-heptane/2-propanol, 97.5/2.5), t_1 = 9.63 min, t_2 = 10.20 min.



2-Methyl-2, 3-diphenylpropanenitrile (4.29)[22]



Prepared from α-methyl benzylcyanide **4.5** (20 mmol, 2.7 ml) and benzyl bromide (21 mmol, 2.4 ml). After purification by flash column chromatography [SiO_2, petroleum ether (40-60 ^{o}C):Et_2O, 2:1], **4.29**[22] was obtained as a yellow oil. Isolated yield 98% (4.3 g, 19.6 mmol).

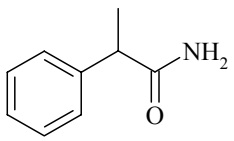
The spectral data were in accordance with the literature.[22] ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 3H, CH_3), 3.19 (s, 2H, CH_2), 7.10-7.15 (m, 2H), 7.28-7.40 (m, 3H), 7.41-7.49 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 138.28, 133.73, 128.95, 127.35, 126.71, 126.50, 125.94, 124.49, 121.73, 47.04, 42.11, 24.59. MS (EI^+) 222 (M+1), 221 (M), 130, 103, 92, 91 (100%), 77, 65, 51. HRMS (EI^+) M^+ for $C_{16}H_{15}N$, calcd. 221.1205, found 221.1214. GC (250 ^oC): t = 15.06 min. HPLC (OJ, *n*-heptane/2-propanol, 99.5/0.5), t_1 = 15.35 min, t_2 = 19.02 min.

General procedure for catalytic nitrile hydrolysis

To a 25 ml round bottom flask equipped with magnetic stirrer were added preformed catalyst **C4.1** (11.1 mg, 0.0256 mmol, 0.5 mol% catalyst loading or more), **C4.3** or $PtCl_2$ (13.3 mg, 0.05 mmol) and racemic or enantiopure **L3.4** (*t*-BuPhPHO, 36.4 mg, 0.2 mmol), nitriles (5 mmol), EtOH (4 ml) and H_2O (2 ml) and the solution was heated to 80 ^oC (in air). After the required reaction time (conversion was checked by TLC and GC), the reaction mixture was allowed to come to RT and the solvent was removed under vacuum. The products were extracted with THF or DCM after evaporating the ethanol/water mixture because of the poor solubility of the catalysts in most organic solvents. After removing the solvent, the solid products were dried overnight under vacuum to yield the corresponding amides, generally pure enough for analysis. If further purification is needed, the products can be crystallized from THF or DCM.

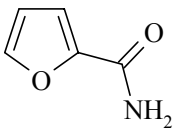
α-Methyl phenyl acetamide (4.6)[23]

Prepared with **C4.1** (5 mg, 0.0117 mmol) from nitrile **4.5** (1.97 g, 15 mmol). After removing the solvent and drying under vacuum, **4.6**[23] was obtained as a white solid. Isolated yield 95% (2.1 g, 14.3 mmol); mp 94-95 ^oC (Lit.[23a-c] 95-96 ^oC). The spectral data were in accordance with the literature. ^{1}H NMR ($CDCl_3$) δ 1.49 (d, *J* = 7.08 Hz, 3H, CH_3), 3.57 (q, *J* = 7.33 Hz, 1H, CH), 5.63 (br, 1H, NH_2), 6.42 (br, 1H, NH_2), 7.24-7.38 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 175.80, 139.82, 127.37, 126.08, 125.76, 45.00, 16.85. MS (EI^+) 150 (M+1), 149 (M), 106, 105 (100 %), 104, 103, 91, 89, 79, 78, 77, 65, 51. GC (250 ^oC): t = 12.05 min, t_{SM} = 15.65 min. HPLC (OD, *n*-heptane/2-propanol, 90/10), t_1 = 12.92 min, t_2 = 17.80 min. For nitrile **4.5**, HPLC (OB-H, *n*-heptane/2-propanol, 95/5), t_1 = 18.28 min, t_2 = 20.98 min.



2-Furamide (4.8) [24]

Prepared from nitrile **4.7** (0.50 g, 5.33 mmol) with catalyst **C4.1** (11.1 mg, 0.0259 mmol). After removing the solvent and drying under vacuum, **4.8** was obtained as an off-white solid. Isolated yield 96 % (0.57 g, 5.1 mmol); mp 140-142 ^oC (lit.[24e,f] 141-142 ^oC). The spectral data were in



accordance with the literature. ^{1}H NMR (DMSO-D_6) δ 6.53-6.59 (1H, m, CH), 7.34 (br, 1H, NH_2), 7.04-7.08 (1H, m, CH), 7.75 (br, 1H, NH_2), 7.76-7.78 (1H, m). ^{13}C NMR (DMSO-D_6) δ 158.33, 146.96, 143.94, 112.54, 110.71. MS (EI^+) 112 (M+1), 111 (M, 100%), 96, 95, 93, 67, 55, 51.

4-Formylbenzamide (4.10) [25]

Prepared from nitrile **4.9** (0.66 g, 5.02 mmol) with catalyst **C4.1** (11.1 mg, 0.0259 mmol). After removing the solvent and drying under vacuum, **4.10** was obtained as a light yellow solid. Isolated yield 97 % (0.73 g, 4.9 mmol); mp 165-167 °C. The spectral data were in accordance with the literature. ^{1}H NMR (DMSO-d_6) δ 7.61 (s, 1H, NH_2), 7.95 (d, J = 8.1 Hz, 2H), 8.04 (d, J = 8.3 Hz, 2H), 8.20 (s, 1H, NH_2), 10.04 (s, 1H, HC=O). ^{13}C NMR (DMSO-d_6) δ 191.85, 166.03, 138.24, 136.73, 128.28, 127.11. MS (EI^+) 150 (M+1), 149 (M, 100%), 148 (M-1), 134, 133, 130, 120, 106, 105, 103, 77, 76, 74, 65, 51, 50.

1, 3-Benzodioxole-5-carboxamide (4.12) [26]

Prepared from nitrile **4.11** (0.74 g, 5.01 mmol) with catalyst **C4.1** (11.2 mg, 0.0261 mmol). After removing the solvent and drying under vacuum, **4.12** was obtained as off-white crystals. Isolated yield 98% (0.81 g, 4.9 mmol); mp 167-168 °C. (lit.[26b] 167-168.5 °C). The spectral data were in accordance with the literature. ^{1}H NMR (DMSO-d_6) δ 6.05 (s, 2H, CH_2), 6.92 (d, J = 8.3 Hz, 1H), 7.25 (s, 1H, NH_2), 7.38-7.48 (m, 2H), 7.84 (s, 1H, NH_2). ^{13}C NMR (DMSO-d_6) δ 166.01, 148.62, 146.17, 127.18, 121.46, 106.65, 106.51, 100.53. MS (EI^+) 166 (M+1), 165 (M), 164 (M-1), 150, 149 (100%), 147, 146, 121, 119, 91, 74, 65, 63, 62, 53, 51.

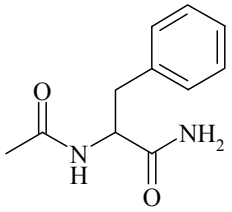
2-Phenyl-2-{[(2*S*,3R,4S,5S,6R)-3,4,5-trihydroxy-6-({[(2*R*,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl]oxy}methyl)tetrahydro-2*H*-pyran-2-yl]oxy} acetamide (4.14)

Prepared from nitrile **4.13** (0.47 g, 1.03 mmol) with catalyst **C4.1** (6.3 mg, 0.0147 mmol) in H_2O (7 ml). After the mixture was heated to 80 °C for 4 h, TLC shows 100% conversion. The reaction mixture was cooled to RT and the solvent was removed. The residue was redissolved in MeOH, the solution filtered; the solvent removed and after drying under vacuum for 12 h, **4.14** was obtained as a white powder. Isolated yield 98% (0.48 g, 1.01 mmol); mp 57-59 °C. $[\alpha]_D$ = -125 ° (c= 0.625, H_2O). ^{1}H NMR (D_2O, 500MHz) δ 3.19-3.24 (m, 2H), 3.26-3.40 (m, 6H), 3.58 (dd, J = 5.37, 12.21 Hz, 1H), 3.73 (dd, J =

5.37, 12.21 Hz, 1H), 3.78 (d, *J* = 11.24 Hz, 1H), 4.06 (d, *J* = 11.23 Hz, 1H), 4.15 (d, *J* = 7.82 Hz, 1H), 4.39 (d, *J* = 7.81 Hz, 1H), 5.25 (s, 1H), 7.32-7.36 (m, 5H, CH). ^{13}C NMR (D_2O) δ 173.98, 133.53, 127.95, 127.47, 126.57, 101.27, 97.42, 77.00, 74.32, 74.12, 73.69, 73.42, 71.53, 71.22, 68.02, 67.72, 66.67, 59.14. MS (ES-MS) 973 (2M + Na^+), 499 (M +1+ Na^+), 498 (M + Na^+, 100%). Anal. calcd for $C_{20}H_{29}NO_{12} \bullet H_2O$: C 48.68%, H 6.33%, N 2.84%. Found: C 48.69%, H 6.63%, N 2.83%.

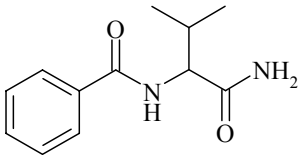
2-(Acetylamino)-3-phenylpropanamide (4.16)[27]

Prepared from nitrile **4.15** (0.10 g, 0.54 mmol) with catalyst **C4.1** (5.5 mg, 0.0128 mmol). After removing the solvent and drying under vacuum for 12 h, **4.16** was obtained as a light yellow solid. Isolated yield 94% (0.105 g, 0.51 mmol); mp 161-163 °C (Lit. 158-160 °C). The spectral data were in accordance with the literature. ^{1}H NMR (DMSO-d_6) δ 3.15 (d, *J* = 7.58 Hz, 2H, CH_2), 3.31 (s, 3H, CH_3), 4.33-4.40 (m, 1H), 6.99 (s, 1H, NH_2), 7.15-7.20 (m, 5H), 7.40 (s, 1H, NH_2), 7.99 (d, *J* = 8.54 Hz, 1H, NH). ^{13}C NMR (DMSO-d_6) δ 172.23, 167.97, 137.17, 128.03, 126.95, 125.11, 52.74, 36.59, 21.45. MS (EI^+) 207 (M+1, 1.1%), 206 (M, 7.2%), 189, 163, 162, 148, 147, 146, 120 (100%), 103, 91, 77, 73, 65, 43. HRMS (EI^+) $C_{11}H_{14}N_2O_2$, calcd. 206.10551, found 206.10488.



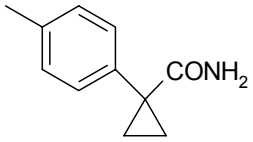
***N*-[1-(Aminocarbonyl)-2-methylpropyl]benzamide (4.18)**[28]

Prepared from nitrile **4.17** (0.185 g, 0.92 mmol) with catalyst **C4.1** (10.1 mg, 0.0235 mmol). After removing the solvent and drying under vacuum for 12 h, **4.18** was obtained as a white solid. Isolated yield 96% (0.195 g, 0.89 mmol); mp 215–217 °C (dec.). (Lit. 216-217 °C). The spectral data were in accordance with the literature. ^{1}H NMR ($CDCl_3$) δ 0.98 (d, *J* = 3.93 Hz, 3H, CH_3), 1.00 (d, *J* = 3.66 Hz, 3H, CH_3), 2.14-2.21 (m, 1H, CH), 4.47 (dd, *J* = 6.96, 8.42 Hz, 1H, CH), 5.48 (s, 1H, NH_2), 6.03 (s, 1H, NH_2), 6.77 (d, *J* = 8.06 Hz, 1H, NH), 7.37-7.49 (m, 3H, CH), 7.75 (d, *J* = 6.96 Hz, 2H, CH). ^{13}C NMR (DMSO-d_6) δ 172.07, 165.37, 133.25, 130.18, 127.15, 126.41, 57.68, 28.98, 18.39, 17.58. MS (EI^+) 220 (M), 177, 176, 161, 106, 105 (100%), 77, 51, 43.



1-(4-Methylphenyl) cyclopropanecarboxamide (4.22)

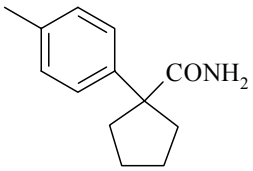
Prepared from nitrile **4.21** (0.79 g, 5.05 mmol) with catalyst **C4.1** (11.3 mg, 0.0273 mmol). After removing the solvent and drying under vacuum, **4.22** was obtained as white crystals. Isolated yield 97% (0.86 g, 4.9 mmol); mp 76-77.5 °C. ^{1}H NMR ($CDCl_3$) δ 1.05 (t, *J* = 3.42 Hz, 2H, CH_2), 1.58 (t, *J* = 3.67 Hz, 2H, CH_2), 2.34 (s, 3H, CH_3),



5.35 (br, 1H, NH_2), 5.92 (br, 1H, NH_2), 7.16 (d, J = 7.33 Hz, 2H), 7.30 (d, J = 7.57 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 175.50, 136.24, 135.44, 129.23, 128.13, 28.11, 19.61, 14.50. MS (EI^+) 176 (M+1), 175 (M, 100%), 174, 160, 158, 132, 131, 130, 128, 117, 116, 115, 105, 91, 89, 77, 65, 51. HRMS (EI^+) M^+ for $C_{11}H_{13}NO$, calcd. 175.0997, found 175.1004. Anal. calcd for $C_{11}H_{13}NO$: C 75.40%, H 7.48%, N 7.99%. Found: C 75.51%, H 7.66%, N 7.96%. GC (250 ^{o}C): t = 12.69 min, t_{SM} = 10.11 min.

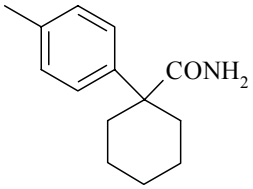
1-(4-Methylphenyl) cyclopentanecarboxamide (4.24)

Prepared from nitrile **4.23** (0.93 g, 5.0 mmol) with catalyst **C4.1** (10.9 mg, 0.0254 mmol). After removing the solvent and drying under vacuum, **4.24** was obtained as white crystals. Isolated yield 99% (1.01 g, 4.98 mmol); mp 110-112 ^{o}C. ^{1}H NMR ($CDCl_3$) δ 1.69-1.74 (m, 2H, CH_2), 1.75-1.81 (m, 2H, CH_2), 1.92-2.12 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 2.36-2.52 (m, 2H, CH_2), 5.20 (br, 1H, NH_2), 5.48 (br, 1H, NH_2), 7.15 (d, J = 6.6 Hz, 2H), 7.26 (d, J = 6.4 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 177.83, 139.55, 135.12, 127.91, 125.14, 57.20, 35.28, 22.45, 19.43. MS (EI^+) 204 (M+1), 203 (M), 160, 159 (100%), 143, 129, 128, 117, 115, 105, 91, 67, 65, 51. HRMS (EI^+) M^+ for $C_{13}H_{17}NO$, calcd. 203.1310, found 203.1354. Anal. calcd for $C_{13}H_{17}NO$: C 76.81%, H 8.43%, N 6.89%. Found: C 76.88%, H 8.61%, N 6.91%. GC (250 ^{o}C): t = 15.28 min, t_{SM} = 12.80 min.



1-(4-Methylphenyl) cyclohexanecarboxamide (4.26)

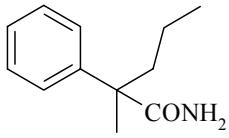
Prepared from nitrile **4.25** (0.16 g, 0.78 mmol) with catalyst **C4.1** (11.9 mg, 0.0277 mmol). After removing the solvent and drying under vacuum, **4.26** was obtained as white crystals. Isolated yield 95% (0.16 g, 0.74 mmol); mp 112-114 ^{o}C. ^{1}H NMR ($CDCl_3$) δ 1.38-1.53 (m, 6H), 1.86-2.00 (m, 2H), 2.16-2.26 (m, 2H), 2.32 (s, 3H, CH_3), 5.36 (br, 1H, NH_2), 6.12 (br, 1H, NH_2), 7.15 (d, J = 8.3 Hz, 2H, CH), 7.30 (d, J = 8.3 Hz, 2H, CH). ^{13}C NMR ($CDCl_3$) δ 177.74, 138.79, 134.92, 128.01, 124.93, 48.90, 32.85, 24.29, 21.33, 19.41. MS (EI^+) 218 (M+1), 217 (M), 174, 173, 143, 131, 115, 106, 105 (100), 91, 81, 77, 55. HRMS (EI^+) M^+ for $C_{14}H_{19}NO$, found 217.1456, calcd. 217.1467. Anal. calcd for $C_{14}H_{19}NO$: C 77.36%, H 8.81%, N 6.45%. Found: C 77.61%, H 9.06%, N 6.41%. GC (250 ^{o}C): t = 16.59 min, t_{SM} = 14.01 min.



2-Methyl-2-phenylpentanamide (4.28) [29]

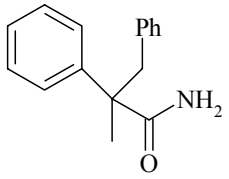
Prepared from nitrile **4.27** (0.48 g, 2.8 mmol) with catalyst **C4.1** (11.1 mg, 0.026 mmol). After removing the solvent and drying under vacuum, **4.28** was obtained as colorless sticky oil. Isolated yield 97% (0.52 g, 2.7 mmol). The spectral data were in

accordance with the literature. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7.08 Hz, 3H, CH_3,), 0.95-1.35 (m, 2H, CH_2), 1.47 (s, 3H, CH_3), 1.85-1.97 (m, 2H, CH_2), 5.33 (br, 1H, NH_2), 6.61 (br, 1H, NH_2), 7.20-7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 178.76, 142.71, 127.01, 125.28, 125.12, 48.83, 39.63, 22.12, 16.15, 13.13. MS (EI^+) 191 (M), 162, 150, 149, 148, 147, 131, 118, 117, 106, 105 (100%), 103, 91, 85, 83, 79, 69, 65, 51, 47. GC (250 °C): t = 13.22 min, t_{SM} = 9.37 min. HPLC (AS, *n*-heptane/2-propanol, 95/5), t_1 = 23.58 min, t_2 = 33.64 min.



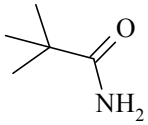
2-Methyl-2, 3-diphenylpropanamide (4.30)

Prepared from nitrile **4.29** (1.11 g, 5.0 mmol) with catalyst **C4.1** (23.3 mg, 0.0543 mmol). After removing the solvent and drying under vacuum **4.30**[29] was obtained as light yellow crystals. Isolated yield 96% (1.15 g, 4.8 mmol); mp 126-128 °C (lit.[29a] 133 °C). The spectral data were in accordance with the literature. ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 3H, CH_3), 3.29 (dd, 2H, CH_2, J = 13.18, 12.94 Hz), 5.41 (br, 1H, NH_2), 5.47 (br, 1H, NH_2), 6.30-6.81 (m, 2H), 7.11-7.12 (m, 3H), 7.21-7.29 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 178.13, 141.54, 135.87, 129.09, 126.96, 126.09, 125.79, 125.71, 124.75, 49.87, 43.50, 21.43. MS (EI^+) 240 (M+1), 239 (M), 196, 195, 194, 180, 179, 178, 167, 165, 152, 149, 148, 147, 136, 135, 132, 121, 120, 118, 117, 115, 105, 104, 103, 92, 91 (100%), 89, 78, 77, 65, 51. HRMS (EI^+) M^+ for $C_{16}H_{17}NO$, calcd. 239.1310, found 239.1321. GC (250 °C): t = 17.89 min, t_{SM} = 15.06 min. HPLC (OD, *n*-heptane/2-propanol, 90/10), t_1 = 10.68 min, t_2 = 15.77 min.



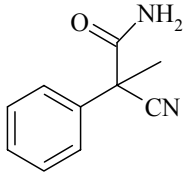
2, 2-Dimethyl propanamide (trimethyl acetamide) (4.32)[30]

Prepared from nitrile **4.31** (0.42 g, 5.08 mmol) with catalyst **C4.1** (11 mg, 0.0256 mmol). After removing the solvent and drying under vacuum, **4.32** was obtained as white waxy-like compound. Isolated yield 79 % (0.40 g, 3.96 mmol); mp 155-156 °C (lit.[30d] 155-157 °C). The spectral data were in accordance with the literature. ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 9H, $3CH_3$), 5.67 (br, 1H, NH_2), 6.07 (br, 1H, NH_2). ^{13}C NMR ($CDCl_3$) δ 180.15, 37.05, 26.08. MS (EI^+) 102 (M+1), 101 (M), 100 (M-1), 87, 86, 85, 83, 69, 58, 57 (100%), 55, 47.



2-Cyano-2-phenylpropanamide (4.36)[31]

Prepared from nitrile **4.34** (36 mg, 0.23 mmol) with catalyst **C4.1** (1.8 mg, 0.0042 mmol). After removing the solvent and drying under vacuum, **4.36** was obtained as a white solid. Isolated yield 68% (27.8 mg, 0.16 mmol); mp 108-110 °C (lit.[31b] 107 °C). ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H, CH_3), 6.02 (br, 2H, NH_2), 6.19 (br, 2H, NH_2), 7.31-7.39 (m, 3H),



7.47-7.50 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 167.76, 134.67, 127.82, 127.46, 124.29, 119.30, 46.78, 23.22. MS (CI^+) 193 ($M+1+NH_4^+$), 192 ($M+NH_4^+$, 100%), Anal. calcd for $C_{10}H_{10}N_2O$: C 68.95%, H 5.79%, N 16.08%, found: C 68.70%, H 5.77%, N 15.67%.

2-Methyl-2-phenylmalonamide (4.38)[32]

Prepared from nitrile **4.34** (60.8 mg, 0.39 mmol) with catalyst **C4.1** (8.3 mg, 0.0193 mmol). After removing the solvent and drying under vacuum, **4.38**[32] was obtained as a white solid. Isolated yield 93% (69.6 mg, 0.36 mmol); mp 145-147 °C (lit.[32a] 150-151 °C). ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3H, CH_3), 6.02 (br, 2H, NH_2), 6.71 (br, 2H, NH_2), 7.20-7.32 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 173.09, 138.08, 126.43, 125.48, 124.62, 55.94, 21.48. MS (CI^+) 210 ($M+1+ NH_4^+$), 194, 193 (M+1, 100 %), 192 (M).

3-(Benzyloxy)-4-cyanobutanamide (4.37)

Prepared from nitrile **4.35** (54 mg, 0.27 mmol) with catalyst **C4.1** (5.6 mg, 0.0131 mmol). After removing the solvent and drying under vacuum, **4.37** was obtained as colorless sticky oil. Isolated yield 52% (30.6 mg, 0.14 mmol). ^{1}H NMR ($CDCl_3$) δ 2.40-2.52 (m, 2H, CH_2), 2.54-2.71(m, 2H, CH_2), 4.07-4.19 (m, 1H, CH), 4.97 (s, 2H, CH_2), 5.78 (br, 1H, NH_2), 5.97 (br,1H, NH_2), 7.29-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 170.34, 134.29, 127.10, 126.46, 124.00, 115.53, 70.91, 70.05, 38.78, 32.71. MS (CI^+) 237 ($M+1+NH_4^+$), 236 ($M+NH_4^+$, 100%), 219 (M+1, 15%), 218 (M), 172, 146.

3-(Benzyloxy)pentanediamide (4.39)

Prepared from nitrile **4.35** (76.8 mg, 0.38 mmol) with catalyst **C4.1** (8.5 mg, 0.0198 mmol). After removing the solvent and drying under vacuum, **4.39** was obtained as an off-white solid. Isolated yield 94% (84.3 mg, 0.36 mmol); mp 170-172 °C (dec.). ^{1}H NMR (DMSO-d_6) δ 2.26 (d, J = 4.76 Hz, 1H, CH_2), 2.31 (d, J = 4.76 Hz, 1H, CH_2), 2.39 (d, J = 7.32 Hz, 1H, CH_2), 2.44 (d, J = 7.32 Hz, 1H, CH_2), 4.22 (p, J = 5.86, 6.26, 6.59 Hz, 1H, CH), 4.52 (s, 2H, CH_2), 6.86 (s, 1H, NH_2), 7.27-7.36 (m, 5H), 7.38 (s, 1H, NH_2).^{13}C NMR (DMSO-d_6) δ 171.06, 137.87, 126.97, 126.29, 126.13, 72.83, 69.64, 39.61. MS (CI^+) 255 ($M+1+NH_4^+$), 254 ($M+NH_4^+$), 238, 237 (M+1, 100%), 236 (M), 235 (M-1), 164, 147.

4.5 References and notes

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The crystallographic data for catalyst **C4.3** in this thesis have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC -

213536. Copies of the data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road Cambridge CB2 1EZ, UK[Fax: (internat.) +44-1223 /336-033; E-mail: deposit@ ccdc.cam.ac.uk].

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